Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	15230	microbial and fermentation	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2005/08/31 20:17
L2	420399	microbial and fermentation and recombiant "protein"	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2005/08/31 20:18
L3	0	microbial and fermentation and "recombiant protein"	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2005/08/31 20:18
L4	2467	microbial and fermentation and "recombinant protein"	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2005/08/31 20:32
L5	37	microbial same fermentation same "recombinant protein"	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2005/08/31 20:18
L6	1019	oscillatingly	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2005/08/31 20:19
L7	35	oscillatingly same cycle	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2005/08/31 20:20
L8	0	oscillatingly and fermentation	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2005/08/31 20:20
L9	0	microbial and fermentation and "recombinant protein" and L6	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2005/08/31 20:21
L10	1971	microbial and fermentation and "recombinant protein" and period	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2005/08/31 20:21
L11	1579	microbial and fermentation and "recombinant protein" and period and cycle	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2005/08/31 20:21
L12	137	microbial and fermentation and "recombinant protein" and period same cycle	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2005/08/31 20:21

L13	33	microbial same fermentation and "recombinant protein" and period same cycle	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2005/08/31 20:21
L14	1097	microbial and fermentation and "recombinant protein" and 435/69.1.ccls.	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2005/08/31 20:32
L15	789	microbial and fermentation and "recombinant protein" and 530/350.ccls.	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2005/08/31 20:32

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arch term postings or to view
search error messages that display as 0* with SET DETAIL OFF.

=> microbial and fermentation and "recombinant protein"
           3   FILE AGRICOLA
           1   FILE ANABSTR
           3   FILE BIOBUSINESS
           7   FILE BIOCOMMERCE
           4   FILE BIOENG
          27   FILE BIOSIS
          76   FILE BIOTECHABS
          76   FILE BIOTECHDS
          10   FILE BIOTECHNO
  15 FILES SEARCHED...
           4   FILE CABA
           1   FILE CANCERLIT
         323   FILE CAPLUS
          14   FILE CEABA-VTB
           7   FILE CEN
           4   FILE CIN
           1   FILE DDFU
           6   FILE DGENE
  27 FILES SEARCHED...
           2   FILE DISSABS
           1   FILE DRUGU
          12   FILE EMBASE
         116   FILE ESBIOBASE
           3   FILE FEDRIP
           1   FILE FROSTI
           3   FILE FSTA
           1   FILE GENBANK
           3   FILE IFIPAT
  43 FILES SEARCHED...
          10   FILE JICST-EPLUS
           8   FILE LIFESCI
          32   FILE MEDLINE
          16   FILE PASCAL
           1   FILE PHIN
          52   FILE PROMT
          14   FILE SCISEARCH
           7   FILE TOXCENTER
        2218   FILE USPATFULL
  67 FILES SEARCHED...
         157   FILE USPAT2
           2   FILE WPIDS
           2   FILE WPINDEX

  38 FILES HAVE ONE OR MORE ANSWERS,   74 FILES SEARCHED IN STNINDEX

L1   QUE MICROBIAL AND FERMENTATION AND "RECOMBINANT PROTEIN"

=> d rank
F1        2218   USPATFULL
F2         323   CAPLUS
F3         157   USPAT2
F4         116   ESBIOBASE
F5          76   BIOTECHABS
F6          76   BIOTECHDS
F7          52   PROMT
F8          32   MEDLINE
F9          27   BIOSIS
F10         16   PASCAL
F11         14   CEABA-VTB
```

F12 14 SCISEARCH
F13 12 EMBASE
F14 10 BIOTECHNO
F15 10 JICST-EPLUS
F16 8 LIFESCI
F17 7 BIOCOMMERCE
F18 7 CEN
F19 7 TOXCENTER
F20 6 DGENE
F21 4 BIOENG
F22 4 CABA
F23 4 CIN
F24 3 AGRICOLA
F25 3 BIOBUSINESS
F26 3 FEDRIP
F27 3 FSTA
F28 3 IFIPAT
F29 2 DISSABS
F30 2 WPIDS
F31 2 WPINDEX
F32 1 ANABSTR
F33 1 CANCERLIT
F34 1 DDFU
F35 1 DRUGU
F36 1 FROSTI
F37 1 GENBANK
F38 1 PHIN

=> file caplus biotechabs medline biosis

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	5.90	6.11

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=> microbial and fermentation and "recombinant protein" and period and cycle
L2 2 MICROBIAL AND FERMENTATION AND "RECOMBINANT PROTEIN" AND PERIOD AND CYCLE

=> d ab bib

L2 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2005 ACS on STN
AB Combined transcriptome and proteome anal. was carried out to understand metabolic and physiol. changes of E. coli during high cell d. cultivation (HCDC). The expression of genes of TCA **cycle** enzymes, NADH dehydrogenase and ATPase, was up-regulated during the exponential fed-batch **period** and was down-regulated afterward. However, expression of most of the genes involved in glycolysis and pentose phosphate pathway was up-regulated at the stationary phase. The expression of most of amino acid biosynthesis genes was down-regulated as cell d. increased, which seems to be the major reason for the reduced specific productivity of **recombinant proteins** during

HCDC. The expression of chaperone genes increased with cell d., suggesting that the high cell d. condition itself can be stressful to the cells. Severe competition for O2 at high cell d. seemed to make cells use cytochrome bd, which is less efficient but has a higher O2 affinity than cytochrome bo3. Population cell d. itself strongly affected the expression of porin protein genes, especially ompF, and hence the permeability of the outer membrane. Expression of phosphate starvation genes was most strongly up-regulated toward the end of cultivation. It was also found that σE (rpoE) plays a more important role than σS (rpoS) at the stationary phase of HCDC. These findings should be invaluable in designing metabolic engineering and **fermentation** strategies for the production of **recombinant proteins** and metabolites by HCDC of E. coli.

AN 2003:195554 CAPLUS
DN 138:398487
TI Combined transcriptome and proteome analysis of Escherichia coli during high cell density culture
AU Yoon, Sung Ho; Han, Mee-Jung; Lee, Sang Yup; Jeong, Ki Jun; Yoo, Jong-Shin
CS Metabolic and Biomolecular Engineering National Research Laboratory, Department of Chemical and Biomolecular Engineering, and BioProcess Engineering Research Center, Korea Advanced Institute of Science and Technology, Daejeon, 305-701, S. Korea
SO Biotechnology and Bioengineering (2003), 81(7), 753-767
CODEN: BIBIAU; ISSN: 0006-3592
PB John Wiley & Sons, Inc.
DT Journal
LA English
RE.CNT 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> microbial and fermentation and "recombinant protein" and cycle
L3 12 MICROBIAL AND FERMENTATION AND "RECOMBINANT PROTEIN" AND CYCLE

=> d ab bib

NSWER 1 OF 12 CAPLUS COPYRIGHT 2005 ACS on STN

AB For many years, high broth viscosity has remained a key challenge in large-scale filamentous fungal **fermns**. In previous studies, we showed that broth viscosity could be reduced by pulsed addition of limiting carbon during fed-batch **fermentation** The objective in this study was to determine how changing the frequency of pulsed substrate addition affects fungal morphol., broth rheol., and recombinant enzyme productivity. To accomplish this, a series of duplicate fed-batch **fermns**. were performed in 20-L fermentors with a recombinant glucoamylase producing strain of Aspergillus oryzae. The total **cycle** time for substrate pulsing was varied over a wide range (30 - 2,700 s), with substrate added only during the first 30% of each **cycle**. As a control, a **fermentation** was conducted with continuous substrate feeding, and in all **fermns**. the same total amount of substrate was added. Results show that the total biomass concentration remained relatively unaltered, while a substantial decrease in the mean projected area of fungal elements (i.e., average size) was observed with increasing **cycle** time. This led to reduced broth viscosity and increased oxygen uptake rate. However, high values of **cycle** time (i.e., 900 - 2,700 s) showed a significant increase in fungal conidia formation and significantly reduced recombinant enzyme productivity, suggesting that the fungi channeled substrate to storage compds. rather than to **recombinant protein**. In addition to explaining the effect of **cycle** time on **fermentation** performance, these results may aid in explaining the discrepancies observed on scale-up to larger fermentors.

AN 2005:195802 CAPLUS

DN 142:446127

TI Effect of **cycle** time on fungal morphology, broth rheology, and recombinant enzyme productivity during pulsed addition of limiting carbon source

AU Bhargava, Swapnil; Wenger, Kevin S.; Rane, Kishore; Rising, Vanessa; Marten, Mark R.

CS Department of Chemical and Biochemical Engineering, University of Maryland, Baltimore County, Baltimore, MD, 21250, USA

SO Biotechnology and Bioengineering (2005), 89(5), 524-529
CODEN: BIBIAU; ISSN: 0006-3592

PB John Wiley & Sons, Inc.

DT Journal

LA English

RE.CNT 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ti 1-47

L3 ANSWER 1 OF 12 CAPLUS COPYRIGHT 2005 ACS on STN
TI Effect of **cycle** time on fungal morphology, broth rheology, and recombinant enzyme productivity during pulsed addition of limiting carbon source

L3 ANSWER 2 OF 12 CAPLUS COPYRIGHT 2005 ACS on STN
TI Flocculation gene expression in genetically modified microorganisms is regulated by medium changes and aids separation of microbes and **fermentation** products

L3 ANSWER 3 OF 12 CAPLUS COPYRIGHT 2005 ACS on STN
TI Combined transcriptome and proteome analysis of Escherichia coli during high cell density culture

L3 ANSWER 4 OF 12 CAPLUS COPYRIGHT 2005 ACS on STN
TI Limiting factors in Escherichia coli fed-batch production of **recombinant proteins**

L3 ANSWER 5 OF 12 CAPLUS COPYRIGHT 2005 ACS on STN
TI Metabolic adaptation of Escherichia coli during temperature-induced **recombinant protein** production: 2. Redirection of metabolic fluxes

L3 ANSWER 6 OF 12 CAPLUS COPYRIGHT 2005 ACS on STN
TI A comparative study of global stress gene regulation in response to overexpression of **recombinant proteins** in Escherichia coli

L3 ANSWER 7 OF 12 CAPLUS COPYRIGHT 2005 ACS on STN
TI 13C NMR Evidence for Pyruvate Kinase Flux Attenuation Underlying Suppressed Acid Formation in Bacillus subtilis

L3 ANSWER 8 OF 12 CAPLUS COPYRIGHT 2005 ACS on STN
TI Metabolic flux distributions in recombinant Saccharomyces cerevisiae during foreign protein production

L3 ANSWER 9 OF 12 CAPLUS COPYRIGHT 2005 ACS on STN
TI Metabolic pathway analysis of recombinant Saccharomyces cerevisiae with a galactose-inducible promoter based on a signal flow modeling approach

L3 ANSWER 10 OF 12 MEDLINE on STN
TI Influence of controlled glucose oscillations on a fed-batch process of recombinant Escherichia coli.

L3 ANSWER 11 OF 12 MEDLINE on STN
TI Use of a cell recycle reactor to increase production of a proteolysis-susceptible peptide secreted from recombinant Saccharomyces cerevisiae.

L3 ANSWER 12 OF 12 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
TI Limiting factors in Escherichia coli fed-batch production of **recombinant proteins**.

=> d ab bib 1-12

L3 ANSWER 1 OF 12 CAPLUS COPYRIGHT 2005 ACS on STN
AB For many years, high broth viscosity has remained a key challenge in large-scale filamentous fungal **fermns**. In previous studies, we showed that broth viscosity could be reduced by pulsed addition of limiting carbon during fed-batch **fermentation** The objective in this study was to determine how changing the frequency of pulsed substrate addition affects fungal morphol., broth rheol., and recombinant enzyme productivity. To accomplish this, a series of duplicate fed-batch **fermns**. were performed in 20-L fermentors with a recombinant glucoamylase producing strain of Aspergillus oryzae. The total **cycle** time for substrate pulsing was varied over a wide range (30 - 2,700 s), with substrate added only during the first 30% of each **cycle**. As a control, a **fermentation** was conducted with continuous substrate feeding, and in all **fermns**. the same total amount of substrate was added. Results show that the total biomass concentration remained relatively unaltered, while a substantial decrease in the mean projected area of fungal elements (i.e., average size) was observed with increasing **cycle** time. This led to reduced broth viscosity and increased oxygen uptake rate. However, high values of **cycle** time (i.e., 900 - 2,700 s) showed a significant increase in fungal conidia formation and significantly reduced recombinant enzyme productivity, suggesting that the fungi channeled substrate to storage compds. rather than to **recombinant protein**. In addition to explaining the effect

of **cycle** time on **fermentation** performance, these results may aid in explaining the discrepancies observed on scale-up to larger fermentors.

AN 2005:195802 CAPLUS
DN 142:446127
TI Effect of **cycle** time on fungal morphology, broth rheology, and recombinant enzyme productivity during pulsed addition of limiting carbon source
AU Bhargava, Swapnil; Wenger, Kevin S.; Rane, Kishore; Rising, Vanessa; Marten, Mark R.
CS Department of Chemical and Biochemical Engineering, University of Maryland, Baltimore County, Baltimore, MD, 21250, USA
SO Biotechnology and Bioengineering (2005), 89(5), 524-529
CODEN: BIBIAU; ISSN: 0006-3592
PB John Wiley & Sons, Inc.
DT Journal
LA English
RE.CNT 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 2 OF 12 CAPLUS COPYRIGHT 2005 ACS on STN
AB This invention relates to flocculation gene expression in genetically modified microorganisms, regulated by medium changes, that aids separation of microbes and **fermentation** products. While the invention focuses on modified yeast strains (hundreds of Saccharomyces cerevisiae strains are claimed), modification of bacteria, fungus, archae, alga and protozoa are also included. The target of genetic engineering in this invention is a series of flocculation genes, including genes FLO2-FLO11, Lg-FLO1, FLO1S, FLO1L, PKC1, sfl1ou, fsu1ou, fsu2ou, tup1ou, cyc8ou, cka2, and FMC1. Regulation of the genes is provided by gene promoters responsive to environmental cues, specifically promoters from genes Mox, HSP30p, pMET3, and ADH. The triggers for regulation of gene expression are provided in the cell culture media at the end of a **fermentation cycle**, including fall of pH, thermal shock, change in sugar, nitrogen or ethanol composition, or phys. excitation. Upon stimulation of the environmental cue, flocculation gene expression is modified, causing the cells to settle quickly to the bottom of the **fermentation** vat, facilitating separation of microbes and **fermentation** product. This invention can be applied to production of a wide range of food or pharmaceutical products including alc. beverages and solution of **recombinant proteins**.
AN 2004:41622 CAPLUS
DN 140:106559
TI Flocculation gene expression in genetically modified microorganisms is regulated by medium changes and aids separation of microbes and **fermentation** products
IN Gomes de Souza, Marcos; Pereira Junior, Haroldo Alves
PA Salinbar S.A., Urug.
SO PCT Int. Appl., 77 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2004005491	A1	20040115	WO 2003-BR89	20030708

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,

FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

BR	2002003754	A	20040525	BR 2002-3754	20020708
EP	1551951	A1	20050713	EP 2003-735214	20030708

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK

PRAI	BR 2002-3754	A	20020708
	WO 2003-BR89	W	20030708

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 3 OF 12 CAPLUS COPYRIGHT 2005 ACS on STN

AB Combined transcriptome and proteome anal. was carried out to understand metabolic and physiol. changes of E. coli during high cell d. cultivation (HCDC). The expression of genes of TCA **cycle** enzymes, NADH dehydrogenase and ATPase, was up-regulated during the exponential fed-batch period and was down-regulated afterward. However, expression of most of the genes involved in glycolysis and pentose phosphate pathway was up-regulated at the stationary phase. The expression of most of amino acid biosynthesis genes was down-regulated as cell d. increased, which seems to be the major reason for the reduced specific productivity of **recombinant proteins** during HCDC. The expression of chaperone genes increased with cell d., suggesting that the high cell d. condition itself can be stressful to the cells. Severe competition for O2 at high cell d. seemed to make cells use cytochrome bd, which is less efficient but has a higher O2 affinity than cytochrome bo3. Population cell d. itself strongly affected the expression of porin protein genes, especially ompF, and hence the permeability of the outer membrane. Expression of phosphate starvation genes was most strongly up-regulated toward the end of cultivation. It was also found that σE (rpoE) plays a more important role than σS (rpoS) at the stationary phase of HCDC. These findings should be invaluable in designing metabolic engineering and **fermentation** strategies for the production of **recombinant proteins** and metabolites by HCDC of E. coli.

AN 2003:195554 CAPLUS

DN 138:398487

TI Combined transcriptome and proteome analysis of Escherichia coli during high cell density culture

AU Yoon, Sung Ho; Han, Mee-Jung; Lee, Sang Yup; Jeong, Ki Jun; Yoo, Jong-Shin

CS Metabolic and Biomolecular Engineering National Research Laboratory, Department of Chemical and Biomolecular Engineering, and BioProcess Engineering Research Center, Korea Advanced Institute of Science and Technology, Daejeon, 305-701, S. Korea

SO Biotechnology and Bioengineering (2003), 81(7), 753-767
CODEN: BIBIAU; ISSN: 0006-3592

PB John Wiley & Sons, Inc.

DT Journal

LA English

RE.CNT 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD

L3 ANSWER 4 OF 12 CAPLUS COPYRIGHT 2005 ACS on STN

AB Fed-batch production of recombinant β-galactosidase in E. coli was studied with respect to the specific growth rate at induction. The cultivations were designed to induce protein production by IPTG at a glucose feed rate corresponding to high (μ = 0.5 h-1) or low (μ = 0.1 h-1) specific growth rate. Protein production rate was approx. 100% higher at the higher specific growth rate, resulting in the accumulation of β-galactosidase up to 30% of the total cell protein. Transcription anal. showed that β-galactosidase-specific mRNA was immediately formed after induction (<5 min), but the amount was the same in both cases and was thus not the initial limiting factor. The content of ribosomes, as represented by rRNA, rapidly decreased with specific growth rate from a relative level of 100%, at the high specific growth rate, to 20% at the low specific growth rate. At high specific growth rate, ribosomes were addnl. degraded upon induction due to the high production level. Translation therefore seemed to be the initial limiting factor of the protein synthesis capacity. The alarmone, guanosine tetraphosphate increased at both high and low feed level inductions, indicating an induction-forced starvation of charged tRNA and/or glucose. The altered physiol. status was also detected by the formation of acetic acid. However, the higher production rate resulted in high-level accumulation of acetic acid, which was absent at low feed rate production Acetic acid production is thus coupled to the high product formation rate and is proposed to be due either to a precursor drain of Krebs **cycle** intermediates and a time lag before induction of the glyoxalate shunt, or to single amino acid overflow, since the model product is relatively poor in glycine and alanine. In conclusion, it is proposed that production at high specific growth rate becomes precursor-limited, while production at low specific growth rate is carbon- and/or energy-limited.

AN 2003:12171 CAPLUS

DN 138:220444

TI Limiting factors in Escherichia coli fed-batch production of **recombinant proteins**

AU Sanden, Anna Maria; Prytz, Ingela; Tubulekas, Ioannis; Forberg, Cecilia; Le, Ha; Hektor, Andrea; Neubauer, Peter; Pragai, Zoltan; Harwood, Colin; Ward, Alan; Picon, Antonia; Teixeira de Mattos, Joost; Postma, Pieter; Farewell, Anne; Nystrom, Thomas; Reeh, Solvejg; Pedersen, Steen; Larsson, Gen

CS The Swedish Centre for Bioprocess Technology, Stockholm Center for Physics, Astronomy and Biotechnology, Stockholm, SE-106 91, Swed.

SO Biotechnology and Bioengineering (2003), 81(2), 158-166
CODEN: BIBIAU; ISSN: 0006-3592

PB John Wiley & Sons, Inc.

DT Journal

LA English

RE.CNT 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 5 OF 12 CAPLUS COPYRIGHT 2005 ACS on STN

AB The impact of temperature-induced synthesis of human basic fibroblast growth factor (hFGF-2) in high-cell-d. cultures of recombinant Escherichia coli was studied by estimating metabolic flux variations. Metabolic flux distributions in E. coli were calculated by means of a stoichiometric network and linear programming. After the temperature upshift, a substantially elevated energy demand for synthesis of hFGF-2 and heat shock proteins resulted in a redirection of metabolic fluxes. Catabolic pathways like the Embden-Meyerhof-Parnas pathway and the tricarboxylic acid (TCA) **cycle** showed significantly enhanced activities, leading to reduced flux to growth-associated pathways like the pentose phosphate pathway and other anabolic pathways. Upon temperature upshift, an excess of NADPH was

produced in the TCA **cycle** by isocitrate dehydrogenase. The metabolic model predicted the involvement of a transhydrogenase generating addnl. NADH from NADPH, thereby increasing ATP regeneration in the respiratory chain. The influence of the temperature upshift on the host's metabolism was investigated by means of a control strain harboring the "empty" parental expression vector. The metabolic fluxes after the temperature upshift were redirected similarly to the production strain; the effects, however, were observed to a lesser extent and with different time profiles.

AN 2002:796103 CAPLUS
DN 138:23758
TI Metabolic adaptation of Escherichia coli during temperature-induced **recombinant protein** production: 2. Redirection of metabolic fluxes
AU Weber, Jan; Hoffmann, Frank; Rinas, Ursula
CS Biochemical Engineering Division, GBF German Research Center for Biotechnology, Braunschweig, 38124, Germany
SO Biotechnology and Bioengineering (2002), 80(3), 320-330
CODEN: BIBIAU; ISSN: 0006-3592
PB John Wiley & Sons, Inc.
DT Journal
LA English
RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 6 OF 12 CAPLUS COPYRIGHT 2005 ACS on STN
AB Global gene regulation throughout the Escherichia coli stress response to overexpression of each of five **recombinant proteins** was evaluated. Reverse-transcriptase polymerase chain reaction-amplified mRNA from induced and control cells were hybridized with a DNA array of Kohara clones representing 16% (700 genes) of the E. coli genome. Subsequently, Northern anal. was performed for quantification of specific gene dynamics and statistically significant overlap in the regulation of 11 stress-related genes was found using correlation anal. The results reported here establish that there are dramatic changes in the transcription rates of a broad range of stress genes (representing multiple regulons) after induction of **recombinant protein**. Specifically, the responses included significantly increased upregulation of heat shock (ftsH, clpP, lon, ompT, degP, groEL, aceA, ibpA), SOS/DNA damage (recA, lon, IS5 transposase), stationary phase (rpoS, aceA), and bacteriophage life **cycle** (ftsH, recA) genes. Importantly, similarities at the microscopic (gene) level were not clearly reflected at the macroscopic (growth rate, lysis) level. The use of such dynamic data is critical to the design of gene-based sensors, the engineering of metabolic pathways, and the determination of parameters (harvest and induction times) needed for successful recombinant E. coli **fermns**. (c) 2000 Academic Press.

AN 2000:903910 CAPLUS
DN 135:191149
TI A comparative study of global stress gene regulation in response to overexpression of **recombinant proteins** in Escherichia coli
AU Gill, R. T.; Valdes, J. J.; Bentley, W. E.
CS Department of Chemical Engineering, University of Maryland, College Park, MD, 20742, USA
SO Metabolic Engineering (2000), 2(3), 178-189
CODEN: MEENFM; ISSN: 1096-7176
PB Academic Press
DT Journal
LA English
RE.CNT 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 7 OF 12 CAPLUS COPYRIGHT 2005 ACS on STN

AB When batch and continuous Bacillus subtilis cultures are provided with a small amount of citrate, acid production ceases, carbon yield increases by more than 2-fold, and the productivity of **recombinant protein** increases. It has been hypothesized that pyruvate kinase activity is attenuated, which in turn lowers glucose flux and minimizes the acid overflow prompted by low Krebs **cycle** capacity. To complement existing enzyme activity, linear programming, and metabolite pool studies, 13C NMR studies were performed. Atom mapping and isotopomer mapping matrix methods were used to select the best glucose label. "Best" was defined such that the NMR spectra of glutamate associated with metabolizing labeled glucose via the different candidate metabolic trafficking scenarios would differ considerably in fine structure (e.g., relative singlet intensities). When expts. were performed with [1-13C]glucose, the observed NMR spectra corresponded well to the one predicted to arise when the metabolic trafficking occurs according to a pyruvate kinase attenuation scenario. This evidence further fortifies the prospects for successfully basing a metabolic engineering strategy on reducing pyruvate kinase activity to better match glycolytic and Krebs **cycle** capacities.

AN 2000:186222 CAPLUS

DN 132:307338

TI 13C NMR Evidence for Pyruvate Kinase Flux Attenuation Underlying Suppressed Acid Formation in Bacillus subtilis

AU Phalakornkule, C.; Fry, B.; Zhu, T.; Kopesel, R.; Ataai, M. M.; Domach, M. M.

CS Department of Chemical Engineering Biotechnology & Health Engineering Program, Carnegie Mellon University, Pittsburgh, PA, USA

SO Biotechnology Progress (2000), 16(2), 169-175
CODEN: BIPRET; ISSN: 8756-7938

PB American Chemical Society

DT Journal

LA English

RE.CNT 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 8 OF 12 CAPLUS COPYRIGHT 2005 ACS on STN

AB A stoichiometric flux balancing anal. was applied to the recombinant yeast cultivation to examine the cellular physiol. and relationship between the production of heterologous protein and metabolic fluxes. The fluxes in the metabolic pathway within a recombinant S. cerevisiae grown on galactose alone or mixts. of galactose and ethanol medium were calculated It is found that an amplification of the PP (pentose phosphate) pathway activity resulted in an improvement of the foreign protein expression and cell yield on ATP. The carbon source used for biosynthesis from TCA **cycle** in the exponential growth phase was 2 and 5-fold higher, resp., as compared with that in the late exponential growth phase and stationary phase in batch culture with galactose min. medium. The metabolism of ethanol together with galactose in the recombinant cell looks like increasing the flux from Acetyl-CoA to TCA **cycle**, and amplifying the flux directing the synthesis of various kinds of precursors such as amino acids and nucleic acid which are necessary for production of a foreign protein. Metabolic flux distribution anal. also shows that the ATP synthesis rate under substrate-level phosphorylation in the mixed carbon source cultivation was lower than that in the sole carbon source (galactose) during the expression of foreign protein. However, the total ATP production rate was higher in the mixed carbon source cultivation.

AN 1997:441121 CAPLUS

DN 127:148372

TI Metabolic flux distributions in recombinant Saccharomyces cerevisiae during foreign protein production

AU Jin, Sha; Ye, Kaiming; Shimizu, Kazuyuki

CS Department of Biochemical Engineering and Science, Kyushu Inst. Technol., Fukuoka, 820, Japan

SO Journal of Biotechnology (1997), 54(3), 161-174
CODEN: JBITD4; ISSN: 0168-1656
PB Elsevier
DT Journal
LA English
RE.CNT 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 9 OF 12 CAPLUS COPYRIGHT 2005 ACS on STN
AB The objective of this work was to develop a signal flow diagram-based modeling approach proposed by Endo et al. (1976) to organize the network of complex metabolic reactions occurring in the living cell, employing directed signal flow diagram in which the enzyme reaction coefficient was defined as the metabolic transfer coefficient Using this concept, a metabolic reaction between substrate A and product B could be regarded as a signal transmittance from A to B. A very simple set of linear equations was then derived to analyze the flow directions of the carbon fluxes and the degree of activation of certain metabolic pathways within a recombinant yeast, in which the specific consumption rate of galactose, the specific rate of change of ethanol and the specific uptake rate of oxygen constituted the three input nodes of the metabolic signal transfer system. The output nodes were the specific growth rate of the cells, the specific production rate of the **recombinant protein** and the specific evolution rate of carbon dioxide. In this way, the effect of the culture conditions on cell growth and **recombinant protein** production under control of the GAL10 promoter could be characterized in terms of the metabolic pathways based on observable variables such as the cell and product concns., and the carbon dioxide and oxygen in the exhaust gas. This approach was successfully applied to an anal. of the metabolic pathways occurring in the fed-batch cultivation of a recombinant yeast where galactose served as both the carbon source for cell growth and as an inducer for expression of the recombinant gene. The expression period was classified into three phases - named the switch, expression, and stationary phases - on the basis of calcns. using signal flow equations. In the switch phase, biomaterials for cell growth were found to be synthesized through the TCA **cycle** and UR loop, and less galactose entered the induction pathway. In the stationary phase, on the other hand, the formation of biomaterials for cell growth occurred mainly through the PP and EMP pathways and the TCA **cycle**. The degree of activation of the induction pathway was reduced in this phase. Unlike in either of the previous two phases, in the expression phase a significant amount of galactose was directed towards the induction pathway to stimulate the expression of the recombinant gene, and the PP pathway played the major role in the synthesis of biomaterials for cell growth.
AN 1996:34349 CAPLUS
DN 124:115511
TI Metabolic pathway analysis of recombinant Saccharomyces cerevisiae with a galactose-inducible promoter based on a signal flow modeling approach
AU Jin, Sha; Ye, Kaiming; Shimizu, Kazuyuki
CS Dep. of Biochemical Engineering and Science, Kyushu Inst. of Technology, Fukuoka, 820, Japan
SO Journal of Fermentation and Bioengineering (1995), 80(6), 541-51
CODEN: JFBIEX; ISSN: 0922-338X
PB Society for Fermentation and Bioengineering, Japan
DT Journal
LA English

L3 ANSWER 10 OF 12 MEDLINE on STN
AB The influence of glucose oscillations on cell growth and product formation of a recombinant Escherichia coli culture producing a heterologous alpha-glucosidase was studied in fed-batch cultures in a laboratory bioreactor. Glucose oscillations were created by an on/off-feeding mode in either fast **cycles** (1 min) or slow **cycles** (4 min)

and compared to a process with constant glucose addition. The study indicates that glucose oscillations influence the product stability and the overgrowth of plasmid-free cells if such cultures are not performed under continuous pressure for selection of plasmid-containing cells. Although the glucose uptake capacity decreased after induction of the recombinant alpha-glucosidase in all cultures performed, the up-growth of plasmid-free cells during the production phase was strongly inhibited by fast oscillations. In contrast, plasmid-free cells grew up when constant feeding or slow **cycles** were applied. Our data suggest that the various feed protocols effect the specific carbon dioxide formation rate differently, with the highest production of carbon dioxide in the cultivations with fast **cycles**. In connection to product formation the initial alpha-glucosidase accumulation was the same in all cultures, but the stability of the product was significantly lower in the cultivation with slow **cycles**. Our results from laboratory experiments are discussed in relation to the mixing situation in large-scale bioreactors.

AN 2000275040 MEDLINE
DN PubMed ID: 10817339
TI Influence of controlled glucose oscillations on a fed-batch process of recombinant Escherichia coli.
AU Lin H Y; Neubauer P
CS Martin-Luther-Universitat Halle-Wittenberg, Fachbereich Biochemie /Biotechnologie, Institut fur Biotechnologie, Halle, Germany.
SO Journal of biotechnology, (2000 Apr 14) 79 (1) 27-37.
Journal code: 8411927. ISSN: 0168-1656.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200007
ED Entered STN: 20000714
Last Updated on STN: 20000714
Entered Medline: 20000706

L3 ANSWER 11 OF 12 MEDLINE on STN
AB Operation of a continuous **microbial** fermentor with cell recycle can significantly reduce degradation-associated loss of a secreted protein product. Under continuous **fermentation** conditions, proteolysis of a recombinant growth hormone releasing factor (GRF) analog secreted by S. cerevisiae was first order with respect to GRF concentration. The maximal GRF concentration was increased from 5 mg/l to 30 mg/l by the use of a cell recycle reactor, and volumetric productivity was increased more than 10-fold to an average of 10 mg/l-1/h-1. A mathematical model shows that increased productivity in the cell recycle reactor results from a reduced degradation rate and a shorter residence time of the product in the fermentor.

AN 91025893 MEDLINE
DN PubMed ID: 1366627
TI Use of a cell recycle reactor to increase production of a proteolysis-susceptible peptide secreted from recombinant Saccharomyces cerevisiae.
AU Siegel R S; Brierley R A
CS Salk Institute Biotechnology/Industrial Associates, Inc. (SIBIA), San Diego, CA 92138.
SO Bio/technology (Nature Publishing Company), (1990 Jul) 8 (7) 639-43.
Journal code: 8309273. ISSN: 0733-222X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Biotechnology
EM 199012
ED Entered STN: 19950809

Last Updated on STN: 19950809
Entered Medline: 19901214

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AB Fed-batch production of recombinant beta-galactosidase in E. coli was studied with respect to the specific growth rate at induction. The cultivations were designed to induce protein production by IPTG at a glucose feed rate corresponding to high (mu=0.5 h-1) or low (mu=0.1 h-1) specific growth rate. Protein production rate was approximately 100% higher at the higher specific growth rate, resulting in the accumulation of beta-galactosidase up to 30% of the total cell protein. Transcription analysis showed that beta-galactosidase-specific messenger RNA was immediately formed after induction (<5 min), but the amount was the same in both cases and was thus not the initial limiting factor. The content of ribosomes, as represented by rRNA, rapidly decreased with specific growth rate from a relative level of 100%, at the high specific growth rate, to 20% at the low specific growth rate. At high specific growth rate, ribosomes were additionally degraded upon induction due to the high production level. Translation therefore seemed to be the initial limiting factor of the protein synthesis capacity. The alarmone guanosine tetraphosphate increased at both high and low feed level inductions, indicating an induction-forced starvation of charged tRNA and/or glucose. The altered physiological status was also detected by the formation of acetic acid. However, the higher production rate resulted in high-level accumulation of acetic acid, which was absent at low feed rate production. Acetic acid production is thus coupled to the high product formation rate and is proposed to be due either to a precursor drain of Krebs **cycle** intermediates and a time lag before induction of the glyoxalate shunt, or to single amino acid overflow, since the model product is relatively poor in glycin and alanin. In conclusion, it is proposed that production at high specific growth rate becomes precursor-limited, while production at low specific growth rate is carbon- and/or energy-limited.

AN 2003:73731 BIOSIS

DN PREV200300073731

TI Limiting factors in Escherichia coli fed-batch production of **recombinant proteins.**

AU Sanden, Anna Maria; Prytz, Ingela; Tubulekas, Ioannis; Forberg, Cecilia; Le, Ha; Hektor, Andrea; Neubauer, Peter; Pragai, Zoltan; Harwood, Colin; Ward, Alan; Picon, Antonia; de Mattos, Joost Teixeira; Postma, Pieter; Farewell, Anne; Nystrom, Thomas; Reeh, Solvejg; Pedersen, Steen; Larsson, Gen [Reprint Author]

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SO Biotechnology and Bioengineering, (January 20 2003) Vol. 81, No. 2, pp. 158-166. print.
CODEN: BIBIAU. ISSN: 0006-3592.

DT Article

LA English

ED Entered STN: 29 Jan 2003
Last Updated on STN: 29 Jan 2003

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